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Evaluation of the Liver Function of Cirrhotic Patients Based on the Formation of Monoethylglycine Xylidide (MEGX) from Lidocaine

By *M. Schinella*[1], *A. Guglielmi*[2], *G. F. Veraldi*[2], *M. Boni*[2], *M. Frameglia*[2] and *M. Caputo*[1]

[1] *Laboratorio di Chimica Clinica ed Ematologia*
[2] *I Divisione Clinicizzata di Chirurgia Generale*
Università degli Studi di Verona, Ospedale Civile Maggiore, Verona, Italy

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Summary: Determination of the functional hepatic reserve is still controversial. Many tests have been proposed, but the assay based on formation of the lidocaine metabolite, monoethylglycine xylidide, seems to offer a promising approach to this problem. In this study we evaluated the effectiveness of the monoethylglycine xylidide test in the clinical evaluation of 31 cirrhotic patients submitted to three different therapeutic options (sclerotherapy, transjugular intrahepatic portosystemic shunt and surgical procedures) and in 1 patient submitted to right hepatectomy for giant hepatic angioma. We found a statistically significant difference between Child A and C patients and between Child B and C patients. The test did not differentiate Child A from Child B patients. We found no correlation between the *Child-Pugh* score, serum bilirubin, albumin and prothrombin time. There were no differences among the three groups of patients that could be statistically related to their therapy. The monoethylglycine xylidide test seems to be an attractive alternative to previous methods for the evaluation of the functional hepatic reserve, but further studies are necessary to assess the prognostic value of the test in cirrhotics, to separate the independent contribution of portosystemic shunting and hepatocyte dysfunction to monoethylglycine xylidide formation, and to evaluate the test as a prognostic index in cirrhotic patients submitted to general surgery.

Introduction

It is difficult to evaluate the functional hepatic reserve in the cirrhotic patient. Conventional static liver function tests lack specificity in predicting disease severity, and dynamic liver function tests could be an attractive alternative to traditional methods (1). In previous papers, the lidocaine metabolite, monoethylglycine xylidide was reported to be a highly sensitive indicator of hepatic dysfunction (2, 3).

Monoethylglycine xylidide is formed from lidocaine by oxidative N-deethylation by the hepatic cytochrome P-450 system (1–4). Prospective studies demonstrated that the monoethylglycine xylidide test in liver donors gives prognostic information on the graft survival in the corresponding recipients (4–6), and may also be suitable for transplant candidate rating and post-transplant follow-up (7–10), even in children (11, 12).

The aim of the present study was to determine the effectiveness of the monoethylglycine xylidide test in the clinical evaluation of cirrhotic patients submitted to sclerotherapy, transjugular intrahepatic portosystemic shunt and general surgery, compared with the *Child-Pugh* classification and score.

Materials and Methods

Between January 1991 and September 1992 we performed the monoethylglycine xylidide test in 41 cirrhotic patients admitted to our surgical unit. Nine patients with monoethylglycine xylidide concentrations above 15 µmol/l due to previous lidocaine treatment were excluded from this study. One patient was affected by a giant hepatic angioma, and all the remaining patients suffered from histologically confirmed liver cirrhosis (tab. 1). Alcohol was the aetiology of liver cirrhosis in most cases (22 cases), 6 patients had posthepatitic cirrhosis, 2 had cryptogenic cirrhosis and 1 had biliary cirrhosis.

Tab. 1. Demographic data of the patients

– Age	range:	29–79 years
	mean:	57.4 years
– Sex	females:	10
	males:	22

Sixteen patients (50%) were referred to our department for bleeding gastro-oesophageal varices (Group 1). In these patients bleeding was controlled by endoscopic sclerotherapy.

Eight patients (25%) (Group 2) were submitted to transjugular intrahepatic portosystemic shunt (see tab. 2) for bleeding recurrence from gastro-oesophageal varices (5 patients), ascites not responsive to medical therapy (2 patients), or reduction of portal hypertension in view of total oesophagectomy for oesophageal carcinoma (1 patient).

Eight patients (25%) (Group 3) were referred to us for surgical evaluation. Table 3 shows the patient group 3 with the diagnosis, the performed operation, the postoperative outcome and the follow-up.

All of the patients were submitted to the normal liver function tests and all of the 31 cirrhotic patients were classified according to *Child-Pugh* criteria (13): this classification includes ascites, encephalopathy, serum bilirubin, albumin and prothrombin time.

In the first group of patients,
4 were class A (*Child-Pugh* score ranging between 5 and 6),
7 were class B (score between 7 and 9) and
5 were class C (score between 10 and 15).

In the second group,
1 patient was *Child* A,
4 patients were *Child* B and
3 patients were *Child* C.

In the third group,
1 patient was class A and
6 patients were class B.

In this latter group we enrolled a non-cirrhotic female receiving a right hepatectomy for giant hepatic angioma.

Venous blood samples for monoethylglycine xylidide determination were collected before and 15, 30 and 60 minutes after a single intravenous bolus of lidocaine hydrochloride (1 mg/kg) injected over a period of 2–4 minutes. Monoethylglycine xylidide was determined in serum by the TDx fluorescence polarization immunoassay system (Abbott Laboratories, Chicago, IL, USA).

The significance of differences between groups was determined by one-way ANOVA, and groups of data were compared using the *Snedecor* F test.

Results

Monoethylglycine xylidide concentrations in all patients at 15, 30 and 60 minutes are shown in figure 1.

The monoethylglycine xylidide concentrations at 30 minutes in patient group 1 (sclerotherapy) ranged between < 6 µmol/l and 62 µmol/l. In this group, monoethylglycine xylidide concentrations at 30 minutes ranged between 8 and 31 in *Child-Pugh* class A, between 7 and 62 in class B and between < 6 and 22 µmol/l in class C.

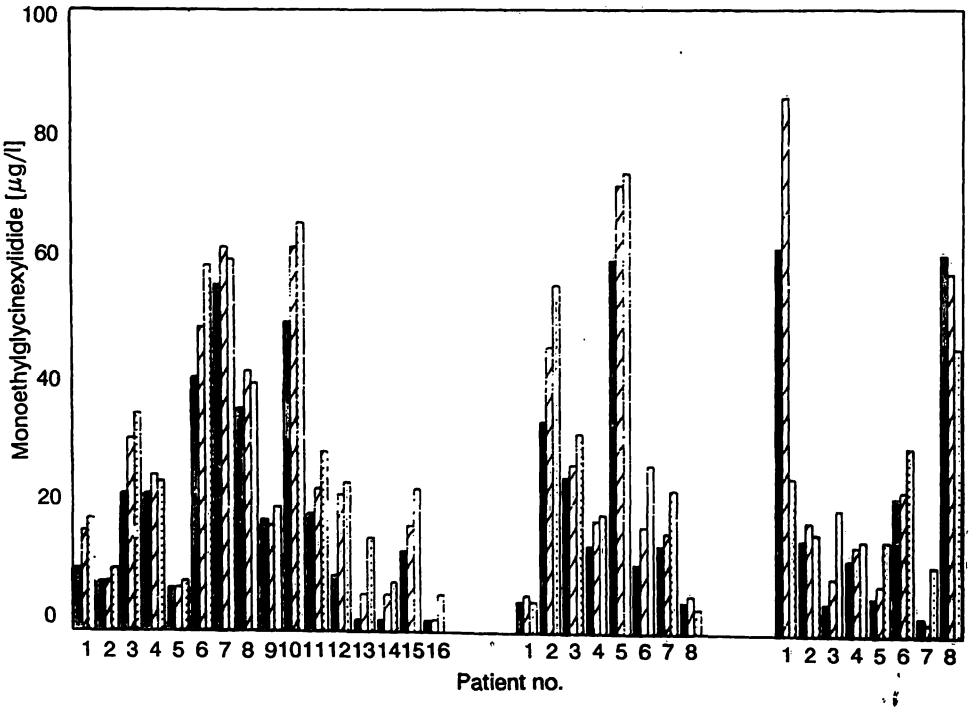

Fig. 1. Monoethylglycine xylidide values in the three patient groups at 15, 30 and 60 min after intravenous lidocaine bolus.
■ 15 min ▨ 30 min ▤ 60 min

In group 2 transjugular intrahepatic portosystemic shunt the 30 minutes monoethylglycine xylidide concentrations ranged between 6 and 62 μmol/l. Monoethylglycine xylidide concentrations at 30 minutes, before the procedure, were 6 μmol/l in the single *Child* A patient, and they ranged between 18 and 62 in the class B patients and between 6 and 17 μmol/l in the class C patients. We compared these results with those obtained three months after the transjugular intrahepatic portosystemic shunt and found no significant differences in monoethylglycine xylidide concentrations (t value = 1.07; p = 0.32). The results obtained in this group of patients are summarized in table 2.

In patient group 3 (operated) the monoethylglycine xylidide concentrations at 30 minutes ranged between 2 and 23 μmol/l for *Child* B patients. The single *Child* A patient had a monoethylglycine xylidide value of 86 μmol/l. In the non-cirrhotic patient with giant hepatic angioma the 30 min monoethylglycine xylidide concentration was 58 μmol/l. The results obtained in this third group of patients are summarized in table 3, where the outcome and the follow-up of single patients is also reported.

Discussion

The goal of this study was to investigate the effectiveness of the monoethylglycine xylidide test in predicting the functional hepatic reserve in cirrhotic patients submitted to three different therapeutic options. We did not find any statistical difference in monoethylglycine xylidide concentrations in the samples at 15, 30 and 60 minutes (see tab. 4); as also stated by other authors (1–4), we think the monoethylglycine xylidide determination at 30 minutes is sufficient for determination of the functional hepatic reserve in cirrhotic patients. We found a statistically significant difference between *Child* A and C patients and between *Child* B and C patients (F = 2.06; p < 0.05). On the basis of the monoethylglycine xylidide we could not differentiate *Child* A from *Child* B patients (mean values 29 μmol/l for both), or find any correlation with the *Child-Pugh* score (see tab. 5). The monoethylglycine xylidide test identified the *Child* C better than *Child* A or B patients. In all the patients there was no statistical correlation between the monoethylglycine xylidide concentrations at 30 minutes and the values of serum bilirubin, albumin and prothrombin time. In table 5 the concentrations of bilirubin, albumin, prothrombin time and *Pugh* score are summarized with the statistical evaluation.

There were no statistical differences in monoethylglycine xylidide values in the three groups of patients

Tab. 2. Results obtained in patients submitted to transjugular intrahepatic portosystemic shunt (Patient group 2)

Patient (a)	Age	Sex	Values before transjugular intrahepatic portosystemic shunt					Values after transjugular intrahepatic portosystemic shunt				
			Bilirubin (μmol/l)	Albumin (g/l)	Pro-thrombin time (%)	*Child-Pugh* classi-fication	*Child-Pugh* score	Monoethyl-glycine xylidide 30 min (μmol/l)	Bilirubin (μmol/l)	Albumin (g/l)	Pro-thrombin time (%)	*Child-Pugh* classi-fication	*Child-Pugh* score	Monoethyl-glycine xylidide 30 min (μmol/l)
P. R.	66	♂	21	22	51	B	8	18	18	28	88	A	6	15
E. M.	77	♀	13	35	80	A	6	6	19	35	68	B	7	16
C. O.	46	♂	16	30	53	B	9	62	21	31	62	B	7	30
B. N.	64	♀	14	33	58	B	8	46	19	33	58	B	8	10
V. G.	52	♂	71	33	60	C	11	16	80	30	60	C	11	14
R. G.	67	♂	35	28	70	B	7	27	40	34	60	B	7	32
C. A.	65	♂	99	20	36	C	14	6	110	25	36	C	11	15
V. L.	79	♂	32	25	59	C	10	17	30	24	60	C	10	18

Tab. 3. Patient group 3 (operated) with post-operative outcome and follow-up

Patient (a)	Age	Sex	*Child-Pugh* classification	*Child-Pugh* score	Monoethylglycine xylidide 30 min (μmol/l)	Diagnosis	Performed operation	Post-operative outcome (30 days)	Follow-up
M. A.	63	♂	A	5	86	Lung cancer	Explorative thoracotomy	Uneventful	Died at 2 months
M. C.	71	♂	B	7	18	Cardial cancer	Total gastrectomy	Uneventful	Alive at 20 months
Gl. L.	52	♀	B	9	23	Gastric cancer	Subtotal gastrectomy	Complicated by infected ascites	Alive at 18 months
V. L.	51	♀	B	9	2	Hepato-cellular carcinoma Hypersplenism	Segmentectomy + Splenectomy	Died from hepatic failure	–
F. D.	61	♂	B	7	9	Oesophageal cancer	Total oesophagectomy	Uneventful	Alive at 19 months
P. V.	64	♂	B	7	14	Hepato-cellular carcinoma	Segmentectomy	Uneventful	Alive at 5 months
M. G.	63	♂	B	8	8	Adenocarcinoma *Vater*'s ampulla	Local excision	Died from hepatic failure	–
O. B.	52	♀	–	–	58	Giant hepatic angioma	Right hepatectomy	Uneventful	Alive at 4 months

Tab. 4. Mean values of monoethylglycine xylidide 15, 30 and 60 min after administration of the lidocaine bolus

	Monoethylglycine xylidide, mean (μmol/l)		
	15 min	30 min	60 min
Group 1	20	25	28
	p = 0.46	p = 0.67	
	p = 0.24		
Group 2	21	25	31
	p = 0.71	p = 0.56	
	p = 0.36		
Group 3	23	31	32
	p = 0.56	p = 0.98	
	p = 0.53		

that could be statistically related to their therapy. Moreover, in the second group of patients, we evaluated the 30 minutes monoethylglycine xylidide concentrations before and three months after transjugular intrahepatic portosystemic shunt, i.e. from a haemodynamic point of view, a side-to-side portocaval shunt; the monoethylglycine xylidide concentrations ranged between 6 and 62 μmol/l before transjugular intrahepatic portosystemic shunt and between 10 and 32 after transjugular intrahepatic portosystemic shunt. From literature data (1, 3), we know that in hepatic cirrhosis the formation of monoethylglycine xylidide is decreased by both portosystemic shunting and hepatocyte dysfunction, but we were not able to differentiate the independent contribution of portosystemic shunting and impaired hepatocyte activity.

Of all the 32 patients, 4 died during a follow-up period ranging from 2 to 19 months. One of these died of cancerous cachexia, the other 3 of liver failure; these 3 patients had 30 min monoethylglycine xylidide concentrations < 8 μmol/l, but the patient number is too small for a statistically relevant prognostic conclusion.

In conclusion, the monoethylglycine xylidide test is quick and easy to perform, it does not require serial blood sample collection but only two specimens of about 1 ml, monoethylglycine xylidide concentrations can be measured within 20 minutes, and the low doses of lidocaine used appear to be safe (1, 5). The monoethylglycine xylidide liver function test seems to be a promising approach to the evaluation of the functional hepatic reserve in cirrhotic patients. Another interesting use of the monoethylglycine xylidide test could be the preoperative assessment of cirrhotic patients prior to general surgery. A larger number of

Tab. 5. Statistical comparison of monoethylglycine xylidide with the mean concentrations of bilirubin, albumin and prothrombin time in the three groups of patients

	Classification	Bilirubin (μmol/l)	Albumin (g/l)	Prothrombin time (%)	Score vs Monoethylglycine xylidide (p)	Monoethylglycine xylidide vs bilirubin, albumin, prothrombin time (p)
Group 1	*Child* A	15	38	64		
	Child B	24	33	58	0.89	0.99, 0.35, 0.95
	Child C	43	24	58		
Group 2	*Child* A	13	35	80		
	Child B	22	28	58	0.75	0.87, 0.31, 0.93
	Child C	67	26	52		
Group 3	*Child* A	25	36	97		
	Child B	25	25	70	0.80	0.63, 0.11, 0.61
	Child C					

patients is needed to evaluate this aspect of the monoethylglycine xylidide test.

Further prospective studies are necessary to fully assess the prognostic value of the test in cirrhotics and to separate the independent contribution of portosystemic shunting and hepatocyte dysfunction in monoethylglycine xylidide formation. It may then be possible to use the test as a predictor of mortality and morbidity, and to assess the extent of intra- and extrahepatic shunting in cirrhotic patients.

References

1. Oellerich, M., Burdelski, M., Lautz, H. U., Schulz, M., Schmidt, F. W. & Herrmann, H. (1990) Lidocaine metabolite formation as a measure of liver function in patients with cirrhosis. Ther. Drug Monit. *12*, 219–226.
2. Oellerich, M., Burdelski, M., Lautz, H. U., Rodeck, B., Duewel, J., Schulz, M., Schmidt, F. W., Brodehl, J. & Pichlmayr, R. (1991) Assessment of pretransplant prognosis in patients with cirrhosis. Transplantation *51*, 801–806.
3. Oellerich, M., Raude, E., Burdelski, M., Schulz, M., Schmidt, F. W., Ringe, B., Lamesch, P., Lamesch, P., Pichlmayr, R., Raith, H., Scheruhn, M., Wrenger, M. & Wittekind, Ch. (1987) Monoethylglycinexylidide formation kinetics: A novel approach to assessment of liver function. J. Clin. Chem. Clin. Biochem. *25* 845–853.
4. Layrargues, G. P., Huet, P. M., Infante-Rivard, C., Villeneuve, J. P., Marleau, D., Duguay, L., Tanguay, S. & Lavoie, P. (1988) Prognostic value of indocyanine green and lidocaine kinetics for survival and chronic hepatic encephalopathy in cirrhotic patients following elective end-to-side portocaval shunt. Hepatology *8* (6), 1506–1510.
5. Schroeder, T. J., Gremse, D. A., Mansour, M. E., Theuerling, A. W., Brunson, M. E., Ryckman, F. C., Suchy, F. J., Penn, ., Alexander, J. W., Pesce, A. J., First, M. R. & Balistreri, W. F. (1989) Lidocaine metabolism as an index of liver function in hepatic transplant donors and recipients. Transplant. Proc. *21*, 229–2301.
6. Oellerich, M., Ringe, B., Gubernatis, G., Pichlmayr, R., Burdelski, M., Lamesch, P., Bunzendhal, H. & Herrmann, H. (1989) Lignocaine metabolism formation as a measure of pre-transplant liver function. Lancet *i*, 640–642.
7. Oellerich, M., Burdelski, M., Lautz, H. U., Binder, L. & Pichlmayr, R. (1991) Predictors of one-year pretransplant survival in patients with cirrhosis. Hepatology *14*, 1029–1034.
8. Lamesch, P., Ringe, B., Oellerich, M., Burdelski, M., Beyrau, R., Gubernatis, G. & Pichlmayr, R. (1990) Assessment of liver function in the early postoperative period after liver transplantation with ICG, MEGX and GAL tests. Transplant. Proc. *22*, 1539–1541.
9. Oellerich, M., Burdelski, M., Beyrau, R., Ringe, B., Lamesch, P., Wonigeit, K., Lautz, H. U., Gubernatis, G., Taki, Y. & Pichlmayr, R. (1989) Lidocaine metabolite formation as a measure of early post-transplant liver function. Hepatology *10*, 625.
10. Oellerich, M., Burdelski, M., Lautz, H. U., Raude, E., Ringe, B., Lamesch, P., Gubernatis, G., Beneking, M., Rodeck, B. & Pichlmayr, R. (1988) Efficiency of the MEGX formation test in liver transplantation. Hepatology *8*, 1220.
11. Gremse, D. A., Schroeder, T. J. & Balistreri, W. F. (1988): Assessment of lidocaine metabolism as a quantitative liver function test in children. Hepatology *8*, 1382.
12. Gremse, D. A., A-Kader, H. H., Schroeder, T. J. & Balistreri, W. F. (1990) Assessment of lidocaine metabolite formation as a quantitative liver function test in children. Hepatology *12*, 565–569.
13. Pugh, R. N. H., Murray-Lyon, I. M., Dawson, J. L., Pietroni, M. G. & Williams, R. (1973) Transection of the oesophagus for bleeding oesophageal varices. Br. J. Surg. *60*, 646–649.

Dr. Michele Schinella
Laboratorio di Chimica Clinica ed Ematologia
Ospedale Civile Maggiore
P. le A. Stefani 1
I-37126 Verona
Italia